REMARKS

Claims 1-52 are pending in the application. Claims 10-41 and 46-52 have been withdrawn by the Examiner as directed to a non-elected invention. Reconsideration of the claims in view of the following Remarks is requested.

I. The Specification Fully Enables the Present Claims

A. The Rejection

Claims 1-9 and 46-52 were rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement. The Examiner asserts that that one of ordinary skill, in light of the prior art, would believe that down-regulation of Dkk-1 would "exacerbate, if not actually induce, any number of cancers" due to upregulation of the Wnt pathway (page 3 of the Final Office Action). The Examiner also states that the enablement provided by the disclosure is not commensurate with the scope of the claims. Applicants traverse this rejection.

B. The Enablement Standard Applicants note that the Examiner "has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *MPEP 2164.04*. A finding that further experimentation is necessary to practice an invention is insufficient to question the enablement of the claims. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *MPEP 2164.01*.

Additionally, "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." *MPEP 2164.01(b)*. Indeed, "[a] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support" (emphasis added). *MPEP 2164.04*.

C. The Claims

The claims are directed to methods of treating insulin resistance or hypoinsulinemia, or methods of repairing or regenerating muscle, comprising administering a Dkk-1 antagonist. In the present case, therefore, the claims satisfy the enablement requirement if the disclosure enables the use as claimed, i.e., the treatment of insulin resistance or hypoinsulinemia, or methods of repairing or regenerating muscle. Applicants submit that, in light of the foregoing standards, the claims are clearly enabled.

D. The Specification Provides Data Establishing the Enablement of the Claims

Insulin resistance is a state characterized by normal or elevated blood glucose levels that persist in the presence of normal or elevated levels of insulin, such that basal or insulin-stimulated glycogen synthesis, or both, are lowered to subnormal levels (page 2, lines 26-30 of the specification).

1. *In vitro* Effects of Dkk-1

The present specification provides data demonstrating that DKK-1 induces insulin resistance. For example, muscle cells treated with Dkk-1 exhibited insulin resistance as compared with controls. (Example 1; page 50, lines 18-19). The specification discloses that administration of Dkk-1 lowered levels of basal and insulin-stimulated glucose uptake in L6 muscle cells, providing evidence directly linking the activity of Dkk-1 to reduced glucose uptake characteristic of insulin resistance. Dkk-1 mediated insulin resistance was also correlated with inhibition of Akt, a known key intermediate in the insulin-signaling pathway (page 50, line 30 through page 51, line 2; and page 52, lines 10-34).

2. *In vitro* Effects of a Dkk-1 Antagonist

The specification also demonstrates generation of an anti-Dkk-1 antibody (Example 2). Administration of the anti-Dkk-1 antibody to L6 muscle cells differentiated in the presence of Dkk-1 resulted in neutralization of Dkk-1 mediated decrease glucose uptake, both in the presence and absence of insulin (page 54, lines 2-6 and Figure 17).

3. In vivo Effects of Dkk-1

The specification also provides *in vivo* evidence demonstrating the effects of Dkk-1 on insulin resistance. Intravenous injection of recombinant Dkk-1 in mice resulted in impaired glucose tolerance and reduced insulin production, as well as decreased insulin-stimulated Akt

activity in muscle (page 48, lines 13-26 and 39-40; Figs. 11A, 11B, and 12B). Transgenic mice overexpressing Dkk-1 in muscle tissue were also shown to exhibit reduced insulin secretion (page 52, lines 35-36).

E. Prior Art and Post-Filing Art Support Enablement of the Claims

Applicants submit herewith Krook et al. (*Diabetes*, 1998, 47:1281-1286), the Abstract of Krook et al. (*Diabetes*, 1997, 46:2110-2114); Shao et al. (*J. Endocrinology*, 2000, 167:107-115), and Strowski et al. (*Endocrinology*, 2004, 145(11):5259-5268). These references collectively disclose that Akt activity is a marker of insulin resistance in NIDDM in some subjects, and that restoration of Akt activity may result in normalization of hyperglycemia.

Specifically, Krook et al. (1997) discloses that improved glucose tolerance resulting from administration of phlorizin "fully restored insulin-stimulated activity of Akt kinase and glucose transport" in diabetic Goto-Kakizaki rats that had previously exhibited a 68% reduction in Akt activity (Abstract).

Krook et al. (1998) discloses that the increase in Akt activity in skeletal muscle upon insulin stimulation was "markedly reduced" in human subjects suffering from NIDDM, when compared to controls (Abstract).

Shao et al. studied the Akt signaling pathway *in vivo* using db/db mice, "a well-established model of obesity and type II diabetes" (page 108, second full paragraph). Shao et al. discloses that, after insulin-stimulation, maximal Akt kinase activy was significantly decreased in the db/db mice compared to non-diabetic littermate controls (Abstract).

Citing Krook et al. 1997 and Krook et al. 1998, Strowski et al. discloses that "[i]nsulin-stimulated activation of Akt in diabetic states in humans and rodents is markedly impaired, and normalization of hyperglycemia correlates with restoration of insulin-stimulated Akt activity" (citing Krook et al., *Diabetes* 47:1281-1286, 1998; and Krook et al., *Diabetes* 46:2110-2114, 1997). Consequently, this post-filing date reference demonstrates that deficiencies in Akt activity continue to be recognized as a significant factor in the etiology of insulin resistance.

F. The Evidence of Record Establishes the Enablement of the Claims

In light of:

1) *in vitro* data demonstrating the ability of Dkk-1 to reduce glucose uptake (a key feature of insulin resistance), inhibit Akt (a key enzyme in the insulin-signaling pathway), and promote muscle differentiation;

2) *in vivo* data demonstrating injection of Dkk-1 in mice resulted in impaired glucose tolerance and reduced insulin production;

3) *in vitro* data demonstrating neutralization of Dkk-1 induced insulin resistance (Akt) on administration of anti-Dkk-1 antibody to Dkk-1 treated muscle cells,

Applicants respectfully submit disclosure working examples, alone and /or combined with the knowledge in the art, reasonably correlates with the scope of the pending claims.

In the present case, the specification provides both *in vitro* and *in vivo* animal models demonstrating the ability of Dkk-1 to invoke the key features of insulin resistance, by impairing glucose tolerance *in vivo* and reducing uptake of glucose into muscle cells *in vitro*. The specification also demonstrates that Dkk-1 inhibits Akt, a key enzyme in the insulin signaling pathway, and whose deficient activity is considered by some studies as a marker of insulin resistance not only *in vitro*, but also in human NIDDM patients and an accepted animal model of insulin resistance. Further, the ability of anti-Dkk-1 antibody to neutralize the effects of Dkk-1 on muscle cells adds support to demonstrate enablement of the claims.

G. Response to Examiner's Arguments

Notwithstanding the data disclosed by the specification, the Examiner argues that the disclosure includes "*no* data involving the use of Dkk-1 antagonists either *in vivo* nor even *in vitro*" (page 3 of the Final Office Action). The Applicants respectfully disagree. As discussed above, the working examples in the specification demonstrate anti-Dkk-1 antibody neutralizes Dkk-1 mediated decreased glucose uptake *in vitro*, both in the presence and absence of insulin (page 54, lines 2-6 and Figure 17).

Moreover, compliance with the enablement requirement "does not turn on whether an example is disclosed," and an "applicant need not have actually reduced the invention to practice prior to filing." *MPEP 2164.02*. Claims can be enabled by disclosure of data from *in vitro* models, if there is a reasonable correlation between the model and the claimed *in vivo* activity; a

"rigorous or invariable" correlation is not required. *MPEP 2163.02.* Applicants submit such a correlation is demonstrated in the examples, at least, by the demonstrated modulation of the Akt enzyme by Dkk-1 and by the anti-Dkk-1 antibody.

In light of the arguments above, the Applicants submit that one of ordinary skill on reading the specification, including working examples, would have reasonably predicted at the time of the invention that the claimed methods of administering a Dkk-1 antagonist would inhibit the effects of Dkk-1 *in vivo* as described in the specification, and result in improved glucose tolerance and glucose uptake, and effectively provide improvement in subjects suffering from insulin resistance.

In further support of Applicants' arguments, Tuttle et al., *Nat Med.*, 2001, Oct;7(10):1133-7 (of record) disclosed that overexpression of Akt1 in β-cells caused a significant increase in levels of serum insulin, as well as improved glucose tolerance and resistance to streptozotocin-induced diabetes (page 52, lines 32-34 of the specification). As discussed above, it was known that reduced Akt activity is a marker of abnormal cells characterized by insulin resistance present in NIDDM. Tuttle et al., however, extended this finding by showing that high Akt activity induced by overexpression resulted in improved glucose tolerance and conferred resistance to diabetes even in normal β-cells.

Similarly, Applicants have discovered that high activity of Dkk-1 inhibits glucose tolerance in normal cells and mice, and have therefore concluded that lowering activity of Dkk-1 by administering an antagonist is reasonably expected to improve glucose tolerance in abnormal cells characterized by insulin resistance.

Applicants respectfully submit that the correlation between the disclosed data and the scope of the claims is therefore reasonable in nature, such that the claims are enabled under the guidelines set forth by the *MPEP.*

Finally, Applicants have also disclosed that intravenous injection of Dkk-1 in mice altered expression of multiple muscle-specific genes, consistent with results seen in L6 muscle cells, providing evidence that Dkk-1 affects muscle differentiation both *in vitro* and *in vivo* (page 48, lines 25-36). As a result, one of ordinary skill would also have reasonably predicted that administering a Dkk-1 antagonist would result in the repair or regeneration of muscle as recited by the claims.

The Applicants reiterate that an actual reduction to practice by administering Dkk-1 antagonists *in vivo* is unnecessary to enable the present claims, if the disclosed data sufficiently correlates with the claim scope. When evaluating the correlation between the disclosed data and the claim scope, a "rigorous or invariable exact requirement is not required" to satisfy the enablement requirement. *MPEP 2163.02*. Rather, the correlation of *in vitro* or *in vivo* animal models with the claim scope need only be reasonable. *Id.*

The Applicants respectfully submit that the foregoing arguments are persuasive evidence that the disclosed data closely correlates with the scope of the claims, and that at the very least, the correlation between the disclosed data and the claim scope can not be dismissed as "unreasonable." Therefore, Applicants believe the claims are fully enabled.

The Examiner argues there is evidence of record that questions the enablement of the claims citing a decreased glucose uptake in L6 muscle cells, but an increased glucose uptake in adipose cells. The Applicants respectfully disagree with the Examiner's assertion that the claimed methods are unpredictable, by disclosing that Dkk-1 exhibited differing results in differing tissue even in "simple" *in vitro* models.

Applicants emphasize, however, that the instant claims are not directed to the effects of Dkk-1 antagonists on a specific body tissue relative to other body tissues, but rather to the treatment of overall insulin resistance in a mammal. As discussed above, the specification is not limited to *in vitro* studies, but also discloses animal models that Dkk-1 impairs glucose tolerance and reduces insulin production *in vivo* in animal models.

In view of the specification, working examples, and knowledge in the art, Applicants submit antagonizing Dkk-1 is reasonably expected to increase glucose tolerance and treat insulin resistance as described in the specification.

The present methods were shown effective in increasing glucose uptake into muscle cells. In this regard, Applicants note that "in normal subjects, the majority of glucose (70-80%) is taken up by skeletal muscle tissue during insulin stimulation. Whole-body insulin resistance can be attributed to diminished glucose uptake by skeletal muscles" (Hallsten et al., *Diabetes* 51:3479-3485, 2002, submitted with this Response).

Applicants have demonstrated that the claimed method of administering a Dkk-1 antagonist result in increased glucose uptake into the skeletal muscle cells responsible for most glucose uptake, and considered a primary factor in the development of whole-body insulin resistance upon development of a glucose-uptake deficiency. Consequently, the Applicants respectfully submit that a difference in the effects of Dkk-1 on muscle cells versus adipose tissue is not sufficient to render the claims non-enabled.

The Examiner has also asserted that the claimed methods are unpredictable due to the complex pathways involving Dkk-1 *in vivo*. As discussed above, Applicants have provided *in vivo* data showing that Dkk-1 administration does in fact predictably impair glucose tolerance, induce changes in glucose uptake, and alter the expression of muscle differentiation markers, all in ways that closely correlate with the effects seen *in vitro* (page 48, lines 25-40 of the specification).

Moreover, despite the complexity of the *in vivo* pathways involving Dkk-1 as asserted by the Examiner, as well as of other polypeptides that can modulate the insulin-signaling pathway, multiple therapeutics having different mechanisms of action at differing locations in the insulin signaling pathway have nevertheless been shown effective in treating insulin resistance.

It is believed that insulin resistance results from a defect in the insulin receptor signaling system, at a site post-binding of insulin to the receptor (page 2, lines 33-38 of the specification). Nevertheless, therapeutics that act upstream of the putative defect, for example, have demonstrated efficacy against insulin resistance (including, for example, insulin itself, as well as the sulfonylurea secretogues of insulin).

As a further example, the thiazolidinedione class of anti-diabetic agents are known agonists of peroxisome-proliferator-activated receptor γ, another enzyme that may play a key role in the regulation of insulin sensitivity, and whose altered expression is also a potential marker of Type II diabetes (page 51, line 33 through page 52, line 4 of the specification).

Consequently, the prior art provides evidence that multiple different classes of therapeutics, exerting influence at varying locations in the insulin pathway, can be efficacious against insulin resistance. Applicants have discovered another molecule, Dkk-1, can also modulate the insulin-signaling pathway, and can impair glucose tolerance *in vivo*. Accordingly,

administration of an antagonist of Dkk-1 would be predicted to regulate the effect of Dkk-1 on insulin resistance.

Applicants reiterate that it is unnecessary to reduce an invention to practice in order to enable the claims, and that disclosure of data from an *in vivo* animal model can provide enablement if there is a reasonable correlation between the model and the claimed activity. For the reasons discussed above, Applicants submit the disclosed *in vivo* data does reasonably correlate with the scope of the claims. Applicants submit the present claims are fully enabled for at least these reasons, and withdrawal of the rejection is respectfully requested.

II. The claims do not lack enablement for lack of safety.

The Examiner also contends that the present invention is not enabled for an additional reason, alleging that one of skill in the art would recognize that administration of a Dkk-1 antagonist could exacerbate or induce cancer. Applicants respectfully disagree, and submit that the present invention has not been shown to be unsafe. Even if the Examiner's assertions regarding the safety of the invention are assumed correct for the sake of argument, Applicants submit that the present claims would not lack enablement under the standards discussed by the *MPEP* and asserted by the case law.

A. Applicants respectfully submit that the rejection of the claims on grounds of alleged safety issues is insufficient to establish a reasonable basis to question the enablement of the claims.

1. The Enablement Standard With Respect to Safety Issues

The *MPEP* states that one "need not demonstrate that the invention is completely safe" to satisfy the enablement requirement. *MPEP 2164.01(c).* The *MPEP* advises that the safety considerations taken into account by a regulatory body such as the FDA are "different from those made by the PTO in determining whether a claim is enabled." *MPEP 2164.05* (citing *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994)("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]")). *Id.* Consequently, in light of the *MPEP's* statements that satisfaction of the enablement requirement does not require a showing of complete safety, Applicants respectfully submit that the present enablement rejection is not consistent with the guidelines set forth by the *MPEP*.

To the extent that a rejection based upon safety considerations could be warranted, however, Applicants respectfully submit that such a rejection is properly made under 35 U.S.C. 101, rather than 35 U.S.C. 112, first paragraph. Indeed, rather than discussing in detail the issue of safety considerations of drugs in an enablement context, the relevant section of the *MPEP* (*MPEP § 2164.06(a) III.*) merely refers the reader to the issue of utility as discussed *MPEP 2107-2107.03*. As will be shown below, this discussion in a utility context delineates the strict limitations placed upon the USPTO's ability to reject claims on grounds of alleged safety concerns.

Specifically, *MPEP 2107.III.* discusses inventions directed to treating human or animal disorders, and notes that

> "[t]he Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States . . . Office personnel should not construe 35 U.S.C. 101 . . . to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans."

Similarly, *MPEP 2107.03* asserts that

> "[t]he Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs. The FDA pursues a two-prong test to provide approval for testing. Under that test, a sponsor must show that the investigation does not pose an unreasonable and significant risk of illness or injury and that there is an acceptable rationale for the study . . . it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness" (emphasis in the original).

The *MPEP* proceeds to provide multiple citations to case law that support the foregoing admonitions against claim rejections based upon issues of safety. *Id.*

2. The Case Law Requires a High Standard for Rejections Based Upon Safety

The Examiner's attention is respectfully directed to one of the cases cited by the *MPEP*, specifically, *In re Anthony*, 162 USPQ 594 (CCPA 1969), a case involving claims directed to an antidepressant. The FDA had suspended a New Drug Application (NDA) for the antidepressant,

stating that clinical experience showed the compound was "unsafe for use under the conditions of use upon the basis of which the application became effective." *Id.* at 600.

In spite of the FDA's refusal to allow the NDA application to proceed due to safety concerns, the court reversed the Examiner's rejection of the claims under 35 U.S.C. 101 for allegedlack of safety. The court stated that "the patent statutes do not establish "safety" as a criterion for patentability of any of the statutory classes of patentable subject matter." *Id.* at 603.

The Examiner's attention is also respectfully directed to a second case cited by the *MPEP*, *In re Watson*, 186 USPQ 11 (CCPA 1973), for additional evidence in support of the Applicants' position. *In re Watson* involved claims directed to germicide compositions for non-selectively killing bacteria in order to improve oral hygiene. The Examiner rejected the claims under both 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph, for alleged lack of safety, and asserted the Applicants failed to demonstrate that "the indiscriminate destruction of bacteria" would be useful. *Id.* at 14. The Examiner based the rejection upon references said to show that "those skilled in the art would not consider . . . appellant's compositions safe for human use."

Nevertheless, the CCPA reversed the rejection by citing the portions of *In re Anthony* quoted above. *Id.* at 19. The court asserted that "in the safety of pharmaceuticals Congress has given primary administrative jurisdiction to federal agencies other than the PTO," and concluded that the evidence of record failed to establish even a *prima facie* case for lack of safety under 35 U.S.C. 101. *Id.* at 20. Significantly, the court held that the 35 U.S.C. 112, first paragraph rejection stood or fell with the utility rejection, and therefore was also improper. *Id.*

3. The Evidence of Record Does Not Meet the Standard Necessary to Question Enablement of the Claims on Safety Grounds.

Applicants respectfully submit that the present claims are enabled even when evaluated in light of the foregoing standards developed by the court, and discussed by the *MPEP*, for cases where an invention does in fact lack safety. The case law indicates generally that issues of safety are not the province of the USPTO. This case law, which has not been reversed or altered by the CAFC, demonstrates that even an FDA finding that a claimed compound is unsafe for its contemplated use is not sufficient by itself to sustain an enablement rejection.

At the very least, Applicants respectfully submit that in light of the case law discussed above, the instant method claims are not rendered non-enabled for lack of safety. Indeed, the Applicants assert there is not even any persuasive evidence of record that administering a Dkk-1 antagonist would be unsafe generally, for reasons that will be discussed *infra*.

Applicants submit that the alleged "undesirable side effects" is not determinative in establishing a reasonable basis to question enablement upon safety grounds.

4. Treatments For Insulin Resistance Do Not Lack Enablement.

Applicants emphasize the serious nature of insulin resistance. Insulin resistance can cause serious long-term complications, including, for example, atheromatous disease, neuropathy, nephropathy, retinopathy, and peripheral vascular disease. Even minimal glucose intolerance is associated with an increased risk of severe cardiovascular disease.

For example, Troglitazone (Rezulin®), is a pharmaceutical approved by the FDA for treating insulin resistance in Type II diabetics. Specifically, Applicants submit an article written by a physician and published in the October 1999 issue of *Medical Software Reviews*. The article reports it was known by 1997 that therapeutic use of troglitazone in humans could cause serious liver toxicity, and was associated with 130 actual reports of liver dysfunction. *Id.*

Despite these safety issues, the FDA initially concluded that the benefits of troglitazone treatment outweighed the risks for patients that did not respond adequately to other anti-diabetic drugs. *Id.* Consequently, while the FDA strengthened labeling requirements for troglitazone in June 1999 and dropped its indication as a first line agent, it did not seek its withdrawal from the market. *Id.*

Applicants also submit herewith an FDA statement dated March 21, 2000, announcing that troglitazone would now in fact be withdrawn from the market. The statement notes that

> "FDA took this action after its review of recent safety data on Rezulin and two similar drugs, rosiglitazone (Avandia) and pioglitazone (Actos), showed that Rezulin is more toxic to the liver than the other two drugs. Data to date show that Avandia and Actos, both approved in the past year, offer the same benefits as Rezulin without the same risk."

The statement also quotes the Director of the FDA's Center for Drug Evaluation and Research, Dr. Janet Woodcock, as saying "[w]e are now confident that patients have safer alternatives in this important class of diabetes drugs."

Dr. Woodcock explicitly linked the decision to withdraw troglitazone not merely to the knowledge of serious side effects, but rather to the combination of such knowledge with the newly reached conclusion that safer alternatives were available. Prior to the evidence leading to the new conclusion, the FDA had determined that the benefits of troglitazone outweighed its risks for at least some patients, as determined in consultation with their physician.

Applicants have discussed above cases where the courts declined to uphold enablement rejections of pharmaceuticals based upon safety grounds, even when the FDA had determined the pharmaceutical was too unsafe to win approval. Although Applicants reiterate that the present methods have not been shown to be unsafe, the Applicants have now also shown, using the publications submitted with this Response, that the FDA itself will approve therapeutics having severe side effects if the benefits of the therapeutic outweigh the risks of side effects.

Indeed, the Applicants have shown that insulin resistance associated with Type II diabetes mellitus is a specific example of a disorder where the FDA has concluded that therapies may provide sufficient benefit, even in light of the possibility of potentially severe adverse effects.

For the foregoing reasons, courts held that in the context of a potentially serious disease such as insulin resistance, the weighing of the benefits and risks of a given therapy is appropriately performed by entities other than the USPTO, such as the FDA, practicing physicians, and their patients. In light of the above discussion, Applicants respectfully submit that one of ordinary skill may clearly consider it appropriate to treat insulin resistance with therapeutics having potentially severe side effects.

5. One of Ordinary Skill Could Practice the Present Invention Without Undue Experimentation.

Additionally, Applicants also note that enablement is determined according to whether one of skill in the art could practice the invention as claimed. A variety of factors are weighed to make this determination, including the level of skill of those in the art. In the present case, one of ordinary skill practicing the claimed methods would possess expertise on insulin resistance,

such as a physician specializing in treating insulin resistance. The Applicants submit that by reading the specification in light of the general knowledge of the art, the skilled physician could weigh the risks and benefits of practicing the present invention on a given patient without undue experimentation. By way of example, the specification provides guidance concerning the dosages of Dkk-1 antagonists for administration, but notes that the actual dosage "will be determined by the physician in the light of the relevant circumstances, including the condition of the mammal, the type of antagonist, the type of indication, and the chosen route of administration" (page 31, lines 7-10).

Similarly, the Applicants submit that evaluation by a physician regarding the relative risks and benefits of a given treatment regimen for insulin resistance would vary from patient to patient. Therefore, the USPTO would necessarily lack the specific information regarding each particular case needed to make appropriate judgments concerning the safety of a treatment for a given patient. Even assuming that the judgments made by a physician for each unique patient required further experimentation, Applicants reiterate that even complex experimentation is not undue, if such experimentation is routinely carried out by those in the art. In the present case, the Applicants submit that physicians treating a complex disorder such as insulin resistance routinely engage in experimentation when planning treatment protocols for patients.

In light of the serious nature of the complications that may result from insulin resistance, Applicants respectfully submit that the evidence of record does not establish that the benefits of the claimed methods would always or almost always be outweighed by the alleged risks, even if these risks are assumed to exist for the sake of argument.

Indeed, and as will now be discussed, Applicants respectfully submit that the evidence of record does not in fact establish the existence of a safety risk provided by the Patent Office is not persuasive, and should not in fact be accepted as real.

B. The evidence does not demonstrate that the claimed methods are unsafe.

Even if sufficient evidence of safety concerns could provide a reasonable basis to question enablement of the present invention, Applicants respectfully submit that the evidence of record is insufficient to provide such a basis.

As an initial matter, Applicants note that of the eight references cited by the Examiner as supporting the role of Dkk-1 antagonists in causing or exacerbating cancer, seven post-date the filing date of the application. "In general, the examiner should not use post-filing date references to demonstrate that the patent is nonenabling." *MPEP 2164.05(a)*. Applicants respectfully submit, therefore, that these references are not relevant to the issue of enablement of the present claims.

Applicants also submit that the remaining reference, Wang et al, is insufficient to establish that the present invention is unsafe. Wang et al. asserts that Dkk-1 may mediate p53 tumor suppression by antagonizing the Wnt pathway, and states that p53 can induce Dkk-1 (Abstract). Nevertheless, Wang et al. discloses that administration of Dkk-1 had no effect on the growth rates of either of two cancer cell lines (page 1847, first paragraph). Applicants submit that, at best, Wang et al. provides conflicting evidence concerning the effect of Dkk-1 on proliferation of cancerous cells, and is therefore insufficient to provide a reasonable basis to question the safety of the claims.

Moreover, Applicants submit that even if use of the remaining seven references is considered proper, the combined teachings of these references also fail to establish a reasonable basis to question the safety of the claimed methods. As was discussed above, the present invention provides data clearly demonstrating that Dkk-1 administration can stimulate glucose uptake, and causes impaired glucose tolerance *in vivo*. Therefore, the Applicants have provided direct evidence linking Dkk-1 to a key feature of insulin resistance. In contrast, none of the 7 remaining references provide direct evidence that Dkk-1 activity prevents carcinogenesis.

Uematsu et al., for example, discloses that Dvl-3 is overexpressed in already cancerous NSCLC cell lines (Abstract), but does not provide any direct evidence that Dkk-1 suppression induces cancerous proliferation. The experiments conducted by Uematsu et al. were focused on the role of Dvl-3, and did not involve Dkk-1.

Chen et al. discloses that overexpression of the oncoprotein SKI correlates with progression of human melanoma, and that SKI activates the Wnt pathway (Abstract). This reference is not directed to Dkk-1 either, and does not provide any direct evidence that Dkk-1 activity prevents carcinogenesis.

Gonzales-Sancho et al. discloses that Dkk-1 is downregulated in colon tumors (page 1101, second paragraph). This reference hypothesizes that "Dkk-1 may act as a tumor suppressor gene in colon cancer," but admits that "[i]t remains to be determined whether extracellular DKK-1 exerts a suppressive effect, given that the pathway is disregulated in this neoplasia as a result of APC or β-catenin mutations that disconnect the downstream cascade from the Wnt receptors" (emphasis added). *Id.* Moreover, the authors note that DKK-1 is overexpressed in some other cancers, including human hepatic blastomas and wilms tumors. *Id.* While this reference hypothesizes that Dkk-1 possesses tumor-suppressive activity that is lost in cancerous colon cells, the disclosed conflicting pattern of Dkk-1 overexpression and underexpression seen among various cancers renders this reference ambiguous. Applicants respectfully submit that Gonzales-Sancho et al. does not provide a reasonable basis for questioning the enablement of the claims.

Lee et al. discloses that Wnt antagonists, including Dkk-1, were known to be downregulated in a variety of cancers, and states that recent evidence shows restoration of the Wnt antagonists may have proapoptotic effects in tumor cells (p. 1247, first full paragraph). Lee et al. does not provide any direct evidence, however, showing that Dkk-1 activity prevents carcinogenesis in healthy cells.

The Le Floch et al. abstract asserts that "inappropriate" activation of the Wnt pathway plays a "critical role at early stages in a variety of human cancers," but discloses that Dvl-2, an activator of the Wnt pathway, "did not alter cell invasion into type I collagen." This abstract does not discuss Dkk-1 at all, and does not provide any direct evidence that Dkk-1 activity prevents carcinogenesis.

Miyoshi et al. discloses that mammary epithelium from transgenic mice expressing certain activating molecules of the Wnt pathway can develop glandular tumors and squamous differentiation (Abstract). Dkk-1, however, is a Wnt suppressor, not a Wnt activator, and therefore was not tested by Miyoshi et al. Miyoshi et al. does not provide any direct evidence that Dkk-1 activity prevents carcinogenesis.

The Behrens et al. abstract states that Wnt signaling is a key pathway in cancer. This abstract does not provide any direct evidence, however, showing that Dkk-1 activity prevents carcinogenesis.

For the foregoing reasons, Applicants respectfully submit the cited references fail to provide persuasive evidence that the claimed methods are unsafe under any circumstance, let alone all circumstances. Withdrawal of the enablement rejection is therefore respectfully requested.

III. The Applicants have rebutted any reasonable basis to question enablement.

As stated above, Applicants do not believe there is a reasonable basis to question the enablement of the claims. Even assuming the existence of a reasonable basis for the sake of argument, however, Applicants submit they have overcome the rejection by presenting "persuasive arguments . . . that one skilled in the art would be able to make and use the claimed invention using the application as a guide," as required by *MPEP 2164.05*. To rebut a *prima facie* case of enablement,"[t]he evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art (emphases in the original). *Id.*

In the present case, Applicants have provided convincing evidence that one of ordinary skill could practice the claimed invention. The Applicants respectfully disagree with the Examiner's position that one of skill in the art would consider it unwise to downregulate Dkk-1. Indeed, the art would discloses that downregulation of Dkk-1 may be useful in cancer therapies. Applicants submitted with the previous Response a reference by Tian et al (*NEJM* 2003; 349:2483-2494). Relying on citations to pre-filing-date references dating from 1986 to 1992, Tian et al. states that lung, breast, prostate cancer, and multiple myeloma were known to cause osteoblastic or osteolytic lesions in bone, and that these lesions are associated with decreased number and function of osteoblasts (first full paragraph). Citing to the pre-filing-date reference Cadigan et al. (*Genes Dev* 1997;11:3286-3305), Tian et al. further notes that the Wnt signaling pathway was known to be important for the growth and differentiation of osteoblasts. *Id.* In light of these teachings of the prior art, Tian et al. proceeded to study patterns of gene expression in myeloma cells, and disclosed that "[t]he production of DKK1, an inhibitor of osteoblast differentiation, by myeloma cells is associated with the presence of lytic bone lesions in patients with multiple myeloma."

The Applicants reiterate that evidence submitted to rebut a reasonable basis to question enablement should be convincing to one skilled in the art, but need not be conclusive. In light of the knowledge in the art as discussed above and the disclosure by the specification that Dkk-1 stimulates the Wnt signaling pathway such that antagonists of Dkk-1 are useful in antagonizing Wnt signaling, one of skill in the art at the time of the present invention would have reasonably predicted that the use of Dkk-1 antagonists to stimulate the Wnt signaling pathway could be useful in therapy.

Additionally, the Applicants also submitted with the previous Response a post-filing-date media article from *Reuters Health* (December 24, 2003) that discusses the findings of Tian et al. Although post-filing-date evidence cannot render an insufficient disclosure enabling, it may be used to prove that a disclosure is enabling, and to substantiate the accuracy of statements made in the specification. *In re Brana*, 34 USPQ2d 1437, 1441 n.19 (Fed. Cir. 1995)(citing *In re Marzocchi*, 169 USPQ 367, 370 n.4 (CCPA 1971)).

The *Reuters Health* article quotes Dr. John Shaughnessy, Professor of Medicine at the University of Arkansas for Medical Science and the lead author of Tian et al., as stating "[w]e now have definitive evidence of a molecular mechanism for myeloma-associated bone destruction. Knowing the molecule that causes the pathology means we can develop drugs that specifically antagonize DKK1 function." Through submission of the *Reuters Health* article, the Applicants have provided direct evidence that one of ordinary skill could consider Dkk-1 antagonists useful. Indeed, the credibility of Shaughnessy's comments is strengthened by his role as lead author of Tian et al., by demonstrating his expertise on Dkk-1 pathways *in vivo*. Not withstanding the Examiner's concerns regarding the fact that Dr. Shaugnessay is commenting on a research paper of which he is a coauthor, Applicants submit that the lead author of a reference is well-qualified to comment on the implications of his own work.

Applicants further note that of the eight references relied on by the Examiner to establish that one of skill would not consider Dkk-1 antagonists useful, four pre-date the *Reuters Health* article discussed above. Significantly, therefore, the Applicants have demonstrated that one of skill in the art believed that therapies using Dkk-1 antagonists could be useful, even after publication of references that the Examiner asserts establishes the non-safety of such therapies. The belief that Dkk-1 antagonists are useful, in spite of these publications, necessarily implies

that one of skill could have reasonably believed in the usefulness of Dkk-1 antagonists at the time of filing, before these publications existed. Consequently, Applicants respectfully submit that the citation of the *Reuters Health* article is both appropriate and highly relevant, as it supports the accuracy of the specification's assertion that Dkk-1 antagonists are useful, and even provides a direct quote establishing that one of ordinary skill at the time of the present invention believed it would be useful to develop Dkk-1 antagonists for purposes of treating human patients.

Applicants respectfully submit that this direct quotation is highly relevant to the enablement rejection, as it conflicts with the assertion that the teachings in the art "would not lead one of skill in the art to conclude that the downregulation of Dkk-1, causing the upregulation of Wnt, would be a good idea." The Applicants have demonstrated that one of skill in the art could believe, and in the case of Dr. Shaughnessy, did in fact believe, that downregulating Dkk-1 may be a useful and appropriate therapy.

By way of contrast, the Applicants respectfully note that the evidence of record does not provide any explicit statement that downregulation of Dkk-1 is unwise under any or all circumstances. As discussed above, none of the references cited by the Examiner state that therapeutic use of Dkk-1 antagonists to reduce insulin resistance would cause or exacerbate cancer, or that the potential risks of such therapy would outweigh the potential benefits. None of the references provide direct evidence that Dkk-1 activity is necessary to prevent carcinogenesis.

Applicants respectfully submit that the Examiner has not met the necessary burden to question the safety of the claimed methods, for at least the foregoing reasons. Withdrawal of the rejection is requested.

IV. Conclusion

The Examiner must weigh all the evidence of record, "including the specification and any new evidence provided by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled." *MPEP 2164.05*. Applicants respectfully submit that when considered as a whole, the evidence for enablement clearly exceeds the alleged evidence of non-enablement.

The Applicants have provided both *in vitro* and *in vivo* data that reasonably correlates with the scope of the claims. The Applicants have demonstrated that rejections based upon safety grounds are, at best, appropriate only in extreme fact patterns that are absent from the present case, and have further demonstrated that the evidence of record concerning non-safety is unpersuasive. While the evidence of record includes ambiguous and indirect evidence regarding the role of Dkk-1 in carcinogenesis, the Applicants have provided unambiguous evidence that Dkk-1 administration can produce insulin resistance and reduce insulin-stimulated glucose uptake, as well as promote muscle cell differentiation. Finally, the Applicants have provided evidence explicitly showing that one of skill in the art could reasonably conclude, and in at least one case has in fact reasonably concluded, that therapeutic use of Dkk-1 antagonists can be useful.

As a result, the Applicants respectfully submit that even assuming the existence of a presumption of nonenablement, the present arguments successfully rebut the presumption. Since the relevant legal and procedural standards place the burden on the USPTO to demonstrate non-enablement, Applicants respectfully submit the evidence of record does not meet the burden necessary to reasonably question the enablement of the claims.

Summary

In view of the foregoing Remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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